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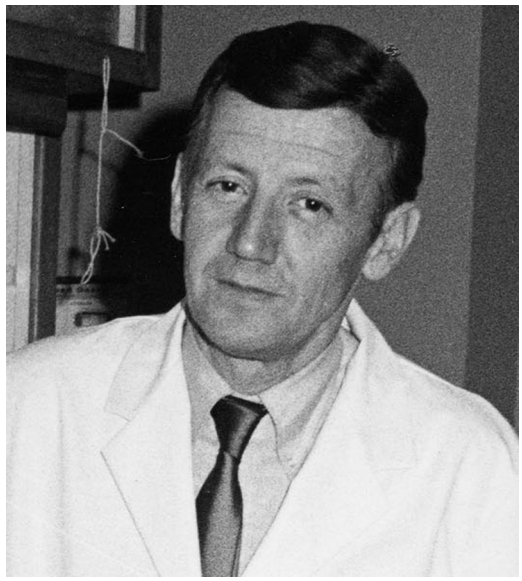
Classics

Vincent Allfrey's Work on Histone Acetylation

Chemical Studies of Histone Acetylation. The Distribution of ϵ-*N*-Acetyllysine in Calf Thymus Histones
(Vidali, G., Gershey, E. L., and Allfrey, V. G. (1968) *J. Biol. Chem.* 243, 6361–6366)

In the 1960s, as a professor at Rockefeller University, Vincent G. Allfrey was mulling over the role of histones in regulating transcription. Much of the focus at that time was on DNA and the passage of genetic information from DNA to RNA to make proteins. Histones were largely considered to be nothing more than simple glues that held DNA together as chromosomes. However, Allfrey was wondering if there was more to histones than met the eye, and he began to question if they were actually involved in actively controlling the passage of information from DNA to RNA. "There was an indication from amino acid analysis at the time that there were some unusual non-standard amino acids in the histones. The burning question at the time was whether these were post-synthetic modifications," explains Joel Gottesfeld at The Scripps Research Institute, who works on histone-modifying enzymes.



Vincent Allfrey. Photo courtesy of the Rockefeller Archive Center.

Allfrey began to delve into the different modifications that appeared on histones—acetylation, methylation, and phosphorylation—to quantify them and understand exactly what their roles were in transcription control. In doing so, Allfrey laid the foundation for modern day epigenetics research. "It's completely appropriate that Vince Allfrey is singled out as being one of the forefathers" of epigenetics, says David Allis at the Rockefeller University, who also focuses on enzymes that modify histones as well as proteins that "read" the modifications.

Allfrey was born in 1921 in New York City. By 1949, he had received M.S. and Ph.D. degrees from Columbia University and went to Rockefeller University, which at that time was called the Rockefeller Institute for Medical Research, as a research associate of Alfred Mirsky. Mirsky is considered to be one of the pioneers in understanding the relationships between protein structure and function. Allfrey became a full professor at the institute in 1963 and remained at Rockefeller for the rest of his career. Allis notes the poignancy of Allfrey's death in 2002 because Allfrey missed seeing the field of epigenetics research explode.

In this JBC Classic from 1968, Allfrey and colleagues delved into the question of how many of the histones were modified at the lysine residues by acetyl groups. Allfrey and colleagues incubated nuclei from the calf thymus with ^{14}C-labeled sodium acetate. It was an experimental procedure which Allis describes as a "Herculean task," and Allfrey's team was able to pull it off only because they were excellent biochemists.

The histones were then separated and analyzed chromatographically, and their amino acid components were quantified. The nomenclature in the paper harks back to the days when histones were classified by their ratio of arginine to lysine in the total amino acid content. f1, now called H1, was lysine-rich; f2a2 and f2b, which are now referred to as H2A and H2B, were slightly lysine-rich; f2a1 and f3, now H4 and H3, were arginine-rich. Allfrey's team found that only two histone fractions, H3 and H4, had significant levels of acetyllysine residues.

The results were "a basic finding in biochemistry," says Gottesfeld. "But the ramifications of the work were enormous", because it showed the existence of acetyllysine in the amino termini

of the H3 and H4 core histones. Future studies would go on to highlight the significance of histone acetylation in regulating chromatin replication during the cell cycle, gene expression, and other genomic processes.

At a time like the 1960s, "Allfrey stuck his neck out to hypothesize that if you were to chemically modify these histone proteins with chemical groups like acetyl, you would be potentially dampening out the positive charge of lysine residues," says Allis. By neutralizing the positive charge on histone proteins, their interaction with the negatively charged DNA backbone would be weakened and the chromatin would be more amenable to gene activation and expression. Allfrey correctly surmised that histones were involved in controlling the dynamics of information transfer from DNA to RNA.

Allfrey and colleagues knew they were onto something for their conclusion in the JBC paper was prescient. They noted, "As a charge neutralization mechanism, acetylation of the histones would be expected to modify DNA-histone interactions, and this may offer a molecular basis for the pronounced changes in histone acetylation and RNA synthesis during the course of gene activation in many cell types."

"Time has shown Allfrey's ideas to be largely correct," says Allis. "He was indeed ahead of all of us who enjoy the rich rewards of his work."

Joel Gottesfeld of The Scripps Research Institute (JBC Associate Editor) nominated the paper as a Classic and Rajendrani Mukhopadhyay (ASBMB Senior Science Writer) wrote the introduction.